

Nivolumab combined with brentuximab vedotin for R/R primary mediastinal large B-cell lymphoma: a 3-year follow-up

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Abstract:

Patients with relapsed/refractory primary mediastinal large B-cell lymphoma (R/R PMBL) have poor responses to salvage therapy. Nivolumab and brentuximab vedotin (BV) showed promising early efficacy in patients with R/R PMBL in the phase I/II open-label, multicenter CheckMate 436 study; we report safety and efficacy findings from the 3-year follow-up. Eligible patients were aged {greater than or equal to} 15 years with R/R PMBL previously treated with either high-dose chemotherapy plus autologous hematopoietic cell transplantation (HCT) or {greater than or equal to} 2 prior multi-agent chemotherapies, and had Eastern Cooperative Oncology Group performance status 0-1 and CD30 expression {greater than or equal to} 1%. Patients were treated with nivolumab 240 mg and BV 1.8 mg/kg once every 3 weeks until disease progression or unacceptable toxicity. Primary endpoint was objective response rate (ORR); secondary endpoints included complete response rate, duration of response, progression-free survival (PFS), and overall survival (OS). Safety was monitored throughout. At final database lock (March 30, 2022), 29 patients had received nivolumab plus BV; median follow-up was 39.6 months. Investigator-assessed ORR was 73.3%; median (range) time to response was 1.3 (1.1-4.8) months. Median PFS was 26.0 months; median OS was not reached. PFS and OS rates (95% CI) at 24 months were 55.5% (32.0%-73.8%) and 75.5% (55.4%-87.5%), respectively. The most frequently occurring grade 3/4 treatment-related adverse event was neutropenia. Consolidative HCT was received by 12 patients, with a 100-day complete response rate of 100.0%. This 3-year follow-up showed long-term efficacy for nivolumab plus BV in R/R PMBL, with no new safety signals. Clinicaltrials.gov: NCT02581631.

Conflict of interest: COI declared - see note

COI notes: Conflicts of interest P.L.Z reports honoraria from AstraZeneca, Bristol Myers Squibb, Gilead, Incyte, Kyowa Kirin, Merck, Novartis, Roche, Takeda, and Sanofi. A.S. reports honoraria from Abbvie, Amgen, AstraZeneca, Bayer, Bristol Myers Squibb, Celgene, Eisai, Gilead, Lilly, Merck Sharp and Dohme, Novartis, Pfizer, Roche, Sandoz, Servier, and Takeda; advisory boards for Bayer, Bristol Myers Squibb, Eisai, Gilead, Merck Sharp and Dohme, and Pfizer, Servier; and consultancy for Incyte and Sanofi. G.G. reports honoraria from Beigene, Clinigen, Ideogen, Incyte, Roche, and Takeda; advisory boards for Genmab, Ideogen, IQVIA, Italfarmaco, Kite-Gilead, Roche, and Takeda; consultancy for Takeda; and meeting/travel support from Roche and Sandoz. P.B. reports honoraria from Takeda. P.M.B. reports advisory boards for TG Therapeutics and consultancy for Abbvie, AstraZeneca, Beigene, Bristol Myers Squibb, Genentech, Gilead, Janssen, Merck, and TG Therapeutics. J. Kuruvilla reports honoraria from Abbvie, Amgen, AstraZeneca, Bristol Myers Squibb, Gilead, Incyte, Janssen, Karyopharm, Merck, Novartis, Pfizer, Roche, and Seattle Genetics; advisory boards for Karyopharm; consultancy for Abbvie, Antengene, Bristol Myers Squibb, Gilead, Karyopharm, Medison Ventures, Merck, Roche, and Seattle Genetics; research support (institution) from AstraZeneca and Merck; and advisory board chair for Lymphoma Canada. D.C. reports advisory boards for OVIBIO and research support (institution) from 4SC, Bayer, Celgene, Clovis, Eli Lilly, Leap, MedImmune, and Roche. J. Kline reports honoraria from Kite-Gilead; consultancy for Merck, Morphosys, Seagen, and Secura Bio; and research support (institution) from Secura Bio. N.A.J. reports honoraria from Abbvie and Beigene; consultancy for Abbvie, AstraZeneca, Beigene, Merck, Roche, and Seattle Genetics; research support from Incyte; and board membership for Lymphoma Canada. N.M-S. reports consultancy for AstraZeneca, C4 Therapeutics, Daiichi Sankyo, Genentech/Roche, Karyopharm, Kyowa Kirin, Ono Pharmaceuticals, and Secura Bio/Verastem; and research support (institution) from AstraZeneca, Bristol Myers Squibb, Celgene, C4 Therapeutics, Corvus Pharmaceuticals, Daiichi Sankyo, Dizal Pharmaceuticals, Genentech/Roche, Innate Pharmaceuticals, Secura Bio/Verastem, and Yingli Pharmaceuticals. J.L. is an employee and has stock in Seagen. R.W. is a Bristol Myers Squibb employee. A.A. is a Bristol Myers Squibb employee. A.J.M. reports honoraria from Affimed, Imbrium Therapeutics, Janpix, Merck, miRagen, Seattle Genetics, and Takeda; consultancy for Affimed, Imbrium Therapeutics, Janpix, Merck, Seattle Genetics, and Takeda; research support (institution) from ADC Therapeutics, Beigene, Bristol Myers Squibb, Incyte, Leukemia Lymphoma Society, Merck, Miragen, NIH/NCI Cancer Center, Seattle Genetics, and Secura Bio; expert testimony for New England Cancer Specialists, review editor for Hematologic Malignancies, SAB member for Lymphoma Hub, and Scientific Review Committee member for Gilead Science.

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4 **Running title**

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Abstract

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Key points

- Nivo + BV showed durable safety and efficacy as salvage in patients with R/R PMBL after 3-year follow-up, with no new safety signals
- High 2-year complete response rates (80–100%) after subsequent HCT indicate potential for nivo + BV as a bridging therapy to transplant

Introduction

Primary mediastinal large B-cell lymphoma (PMBL) is a mature, aggressive large B-cell lymphoma of thymic origin. PMBL occurs most frequently in young adults, with a median patient age of 35 years and a slight female predominance, and constitutes 2%–4% of non-Hodgkin lymphoma (NHL).^{1,2} First-line treatment for PMBL typically consists of chemoimmunotherapy with rituximab and chemotherapeutic agents.³ After first-line chemoimmunotherapy, the 3-year progression-free survival (PFS) rate is 89.4%,⁴ and 5-year PFS and event-free survival are generally above 80%.^{5,6} In contrast, patients with relapsed/refractory (R/R) PMBL have poor outcomes; 2-year PFS rate after first disease progression is reported as 29%.⁴ The objective response rate (ORR) to salvage chemotherapy was 25% and the 2-year overall survival (OS) rate after diagnosis of R/R disease was 15%–29%.^{7,8} These outcomes highlight a need for new therapeutic strategies for patients with R/R PMBL.

The checkpoint inhibitor nivolumab is a human immunoglobulin G4 monoclonal antibody that binds to the programmed death 1 (PD-1) protein receptor and blocks its interaction with programmed death ligand (PD-L) 1 and PD-L2.^{9,10} Brentuximab vedotin (BV), an anti-CD30 antibody conjugated to monomethyl auristatin E, induces apoptosis of CD30+ tumor cells by disrupting the microtubule network and inhibiting cell division.^{11,12} Nivolumab in combination with BV has shown promising efficacy in patients with R/R classical Hodgkin lymphoma (cHL), a disease that shares clinical and molecular features with PMBL, including abnormalities in chromosomes 9p and 2p, high mutational density, and expression of CD30.^{13–16} Phase I/II trials of nivolumab in combination with BV in R/R cHL have reported ORRs of 82%–89%,^{17,18} and a recent long-term follow-up of patients with R/R cHL treated with nivolumab plus BV showed durable efficacy, with an 85% ORR and an estimated 3-year PFS rate of 77% at a median follow-up of 34.3 months.¹⁹

In the treatment of R/R PMBL, BV monotherapy has shown an ORR of just 13.3% in a phase II study.²⁰ An optimal treatment approach for R/R PMBL is not well established, but therapies with anti-PD-1 agents, such as nivolumab with or without BV and pembrolizumab, are included as treatment options based on their clinical efficacy in this setting.³ The phase Ib KEYNOTE-013 and phase II KEYNOTE-170 studies showed ORRs of 48% and 45%, respectively, in adult patients with R/R PMBL treated with pembrolizumab.²¹ The CheckMate 436 study is an open-label, multicenter, multicohort, phase I/II study of nivolumab in combination with BV in patients with R/R NHL. Initial results from 11.1 months median follow-up of the R/R PMBL cohort showed a 73% ORR, and a 37% complete response (CR) rate per investigator; 6-month PFS and OS rates were 63.5% and 86.3%, respectively.²² The

safety profile was manageable and there were no treatment-related deaths.²² Here, we report the results from the 3-year follow-up of the PMBL expansion cohort in CheckMate 436.

Methods

The methods for the Checkmate 436 study PMBL cohort were previously reported by Zinzani et al.²² and are briefly described here.

Trial design and ethics

Checkmate 436 (ClinicalTrials.gov identifier: NCT02581631) is an open-label, multicenter, multicohort, phase I/II study of nivolumab in combination with BV in adult patients with R/R NHL. The study consists of a phase I dose evaluation and a phase II efficacy and safety evaluation in expansion cohorts with R/R NHL subtypes: PMBL, diffuse large B-cell lymphoma, peripheral T-cell lymphoma, cutaneous T-cell lymphoma, and mediastinal gray zone lymphoma. Results from the R/R PMBL cohort are reported here.

All patients provided written informed consent. The study protocol was approved by the Ethical Review Committee of all participating centers and was carried out in accordance with the principles of the Declaration of Helsinki.

Patients

Eligible patients in the PMBL cohort were aged 15 years or older, had Eastern Cooperative Oncology Group (ECOG) performance status scores of 0–1, had CD30 expression $\geq 1\%$ in the tumor or tumor-infiltrating lymphocytes (as measured by local immunohistochemistry), and had measurable disease per Lugano 2014 classification.²³ Patients were required to have R/R disease after high-dose chemotherapy with autologous hematopoietic cell transplantation (auto-HCT) or more than two prior multi-agent chemotherapies (for patients ineligible for auto-HCT).

Treatment

Doses for the phase II expansion cohorts were determined during the phase I dose-evaluation assessments.²² Patients received nivolumab 240 mg (flat dose) and BV 1.8 mg/kg once every 3 weeks and were treated until disease progression or unacceptable toxicity. Treatments were administered intravenously over 30 minutes. Patients received nivolumab on cycle (C) 1 day (D) 8 and BV on C1D1. In subsequent cycles both treatments were given on the same day, with BV administered before nivolumab infusion, separated by a 30-minute rest period. Per protocol, dose modifications per body weight change were allowed for BV, and reduction to 1.2 mg/kg was permitted for prespecified toxicities. No dose modifications were permitted for nivolumab, but doses could be delayed for specified treatment-related adverse events (TRAEs). Follow-up visits were carried out 35 ± 7 days after the last dose

and 80 ± 7 days after the first follow-up, with subsequent follow-up for survival every 3 months until death or loss to follow-up.

Endpoints and assessments

The primary efficacy endpoint of the study was ORR assessed by investigator, with overall response defined as the best overall response (BOR) of confirmed CR, or partial response (PR) as assessed by Lugano 2014 classification²³ between the date of first dose and either documented progression or subsequent therapy (including auto-HCT or allogeneic HCT). Secondary endpoints included duration of response (DOR), CR rate, duration of CR, PFS, and OS. DOR was calculated as time from initial documented CR or PR to the first evidence of progressive disease, relapse, or death. PFS was defined as the time from the first dose of study drug until the first evidence of progressive disease, relapse, or death. Patients who were progression-free and alive or had unknown status were censored at the last tumor assessment, and patients who received subsequent therapy (including HCT) prior to documented progression were censored on the last tumor assessment date prior to subsequent therapy. OS was defined as the time from first dose of study drug until the date of death for any reason; if the patient was alive or vital status was unknown, patients were censored at the last date they were known to be alive.

CD30 and PD-L1 expression were measured in baseline tumor biopsy samples using validated immunohistochemistry assays (CD30, Mosaic laboratories; PD-L1, BMS and DAKO North America). PD-L1 and CD30 expression status was defined as percentage of tumor cells exhibiting cell surface staining of each biomarker in a minimum of 100 evaluable tumor cells.

Patients discontinuing treatment for any reason entered the follow-up phase of the study and were monitored for long-term safety, survival status, disease progression, subsequent anticancer therapy, and occurrence of other primary malignancies. The first two follow-up visits were conducted in person and subsequent follow-up visits were conducted in person or by phone. All participants were followed for survival at least every 3 months until death or loss to follow-up.

Safety was monitored throughout the study. All AEs were tabulated using the worst grade per Common Terminology Criteria for Adverse Events v4.03 criteria and Medical Dictionary for Regulatory Activities preferred term. Safety analyses were performed per cohort and in all treated patients combined.

Statistical analysis

A sample size of 30 patients with R/R PMBL was chosen based on a two-sided 80% confidence interval (CI) for an ORR of 37%–63% by assuming an observed ORR of 30%.

ORR and CR were summarized by binomial response rate using the Clopper–Pearson method. PFS was summarized using the Kaplan–Meier product-limit method. Descriptive statistics of safety were presented. All statistical analyses were performed using SAS version 9.4.

Data sharing policy

The Bristol Myers Squibb policy on data sharing may be found at <https://www.bms.com/researchers-and-partners/independent-research/data-sharing-request-process.html>.

Results

Baseline demographics and disease characteristics, patient disposition, exposure

A total of 30 patients with R/R PMBL were enrolled and treated. The median (range) patient age was 36 (19–83) years. Most patients had refractory disease at enrollment, and all had received prior first-line rituximab-based therapy (**Table 1**). At the final database lock (March 30, 2022), all 30 patients had ended the treatment period. The most frequent reasons for treatment discontinuation were maximum clinical benefit ($n = 13$, 43.3%) and disease progression ($n = 8$, 26.7%) (**Table S1**). Twenty-four (80%) patients with R/R PMBL were continuing in the study (either for continued treatment or follow-up). Of the patients not continuing in the study, 4 (13.3%) died, 1 (3.3%) withdrew consent, and 1 (3.3%) was lost to follow-up. Nivolumab was received by 29 patients; 1 additional patient received BV in C1D1 but discontinued before the first nivolumab dose. The median (range) number of doses received was 5 (1–35) and 5 (1–20) for nivolumab and BV, respectively, with 22 (75.9%) patients receiving relative dose intensity between 90% and 110% for nivolumab.

Efficacy

The ORR was 73.3% (95% CI, 54.1%–87.7%), with 40.0% and 33.3% of patients achieving CR and PR, respectively (**Table 2**). The median (range) time to response was 1.3 (1.1–4.8) months, with 3.2 (1.2–11.0) months to CR. At a median follow-up of 39.6 months, the median DOR was not reached. Four patients remained progression-free without subsequent HCT (**Figure 1**). Median PFS was 26.0 months (95% CI, 2.6 to not reached); PFS rates at 6, 12, 18, and 24 months were 63.5% (95% CI, 42.5%–78.6%), 55.5% (95% CI, 32.0%–73.8%), 55.5% (95% CI, 32.0%–73.8%), and 55.5% (95% CI, 32.0%–73.8%), respectively (**Figure 2**). Median OS was not reached; OS rates at 6, 12, 18, and 24 months were 86.3% (95% CI, 67.5%–94.6%), 79.1% (95% CI, 59.3%–90.0%), 75.5% (95% CI, 55.4%–87.5%), and 75.5% (95% CI, 55.4%–87.5%), respectively (**Figure 3**).

Evaluation of response status per investigator versus CD30 expression in baseline tumor biopsies showed that patients across the entire range of CD30 expression were able to achieve CR or PR (**Figure S1**). All treated patients had $\geq 5\%$ PD-L1 positive cells at baseline, however a PD-L1 expression subgroup deriving a higher or lower response benefit could not be identified (**Figure S2**).

Subsequent therapy and consolidative HCT

A total of 18 (60%) patients received subsequent anticancer therapy, including 7 patients (23%) who received non-palliative radiotherapy and 6 (20%) who received systemic therapy. Among these patients, 13 received subsequent anticancer therapy without a prior reported progression event. Consolidative HCT was received by 12 (40%) patients: 6 (20%) receiving auto-HCT and 6 (20%) receiving allogeneic HCT (**Table S2**). Patients received 3–20 cycles of nivolumab plus BV prior to auto-HCT and 5–14 cycles of nivolumab plus BV prior to allogeneic HCT. Of the patients receiving auto-HCT or allogeneic HCT, 3/6 (50%) patients achieved CR at the time of transplantation in each group; patients not achieving CR had a BOR of PR. After 100 days, 6/6 (100%) and 5/5 (100%) patients assessed in the auto-HCT and allogeneic HCT groups, respectively, had CR. Two patients continued to investigational trials for chimeric antigen receptor (CAR) T cell therapy.

Safety

A total of 25 (83.3%) patients experienced at least one TRAE, with 16 (53.3%) patients experiencing a grade 3/4 TRAE (**Table 3**). The most frequently occurring any-grade TRAEs were neutropenia (43.3%), pyrexia (30.0%), and arthralgia (20.0%). Neutropenia was also the most frequently occurring grade 3/4 TRAE (40.0%). There were no grade 5 TRAEs related to the study drug. The most common immune-mediated AEs were diarrhea/colitis and rash (**Table S3**).

Nine patients discontinued study treatment due to AEs; among these patients, 4 initially discontinued BV and remained on nivolumab, 4 discontinued both study drugs simultaneously, and one died. Six patients discontinued study treatment due to treatment-related AEs, most commonly peripheral neuropathy (**Table S4**). There were 8 deaths reported, 2 of which occurred within 30 days of the last dose. The primary cause of death was disease progression ($n = 5$); other causes included sepsis ($n = 1$), cardiovascular disease ($n = 1$), and neurologic complications after allogeneic HCT ($n = 1$). No deaths were considered related to the study drug by the investigator.

Discussion

This 3-year follow-up of the CheckMate 436 study of nivolumab plus BV for the treatment of R/R PMBL represents one of the studies using checkpoint inhibitors that have the longest follow-ups in this setting, and shows one of the highest ORRs for this treatment setting.^{21,24} Efficacy results with nivolumab plus BV were consistent with previous reports from CheckMate 436,²² with a 73.3% ORR and a 40.0% CR rate. The 2-year OS rate of 75.5% indicates durable efficacy of nivolumab plus BV as salvage therapy in R/R PMBL. Safety data were also consistent with previous reports of CheckMate 436,²² with neutropenia, thrombocytopenia, and peripheral neuropathy among the most frequently occurring grade 3/4 TRAEs. This 3-year follow-up showed an increase in overall incidence of neutropenia compared with the previous report (any grade: 43% vs 30%; grade 3/4: 40% vs 30%).²² The reason for this increased incidence is unclear, and the association of neutropenic events with extended exposure to nivolumab has not been examined in NHL. Neutropenia has been observed after anti-PD-1 monotherapy in patients with R/R PMBL.²¹

Patients with R/R PMBL treated with nivolumab plus BV in this study achieved a 2-year PFS rate of 55.5%, which represents approximately twice the PFS rates previously reported for this population,⁴ and ORR and OS rates are more than doubled compared with prior reports of salvage chemotherapy in this population.^{7,8} Patients with R/R PMBL in the CheckMate 436 study were also able to achieve CR or PR across a range of CD30 expression levels.

These results also align with previous studies showing long-term efficacy of nivolumab plus BV in patients with R/R cHL, which reported a 3-year ORR of 85% and an OS rate of 93%.¹⁹ The ORR for nivolumab plus BV in this study was also higher than the 13.3% ORR for BV monotherapy in R/R PMBL²⁰ and the 48% and 45% ORRs for anti-PD-1 monotherapy reported in the KEYNOTE-013 and KEYNOTE-170 trials, although direct comparisons between these studies should be approached with caution due to differences in design.²¹

The distinct anti-tumor mechanisms of action of BV and anti-PD-1 agents provide strong rationale for combining these therapies.²⁵ BV complements the checkpoint inhibition of anti-PD-1 agents not only by disrupting the microtubule network of tumor cells and triggering apoptosis,¹² but also through activation of innate and adaptive immune cells. In mouse models, proinflammatory anti-tumor immune responses resulting from BV treatment are potentiated by combination anti-PD-1 therapy.^{26,27} Recent studies have also indicated clinical synergy between nivolumab and BV in R/R cHL. In the CheckMate 205 study, nivolumab showed efficacy in patients with R/R cHL who had been previously treated with BV,¹⁰ and a retrospective analysis of patients with R/R cHL treated with nivolumab plus BV indicated promising efficacy.²⁸ R/R PMBL shares clinical and molecular features with R/R cHL,

including high mutational density and expression of CD30,^{13-15,29} and data reported here for CheckMate 436 possibly indicate a similar synergy in patients with R/R PMBL.

Preliminary data showed that 4 patients in this study had a durable PFS without consolidative HCT; however, 60% of all patients in the study received subsequent anticancer therapy, and 40% received either allogeneic or auto-HCT. Further analysis is warranted to explore survival outcomes in patients treated with nivolumab plus BV with versus without consolidation therapy.

In patients with R/R PMBL, response to salvage therapy is a prognostic factor for the success of subsequent HCT, but patients treated with ifosfamide, carboplatin, and etoposide (ICE) or rituximab plus ICE as salvage therapy before auto-HCT previously showed an estimated 3-year OS rate of just 65%.³⁰ In the CheckMate 436 study, the ORR was 73.3%, with a 24-month OS rate of 55.5%. Of the patients treated with nivolumab plus BV in the PMBL cohort who underwent HCT, CR rates were high, with a 100% CR rate after 100 days and 2-year CR rates of 100% and 80% for auto- and allogeneic HCT, respectively. Results from the CheckMate 436 study indicate that nivolumab plus BV can potentially be a bridging therapy prior to auto- and allogeneic HCT for patients with R/R PMBL. In addition, CAR T cell therapy is emerging as an effective treatment option for R/R lymphomas,³¹⁻³⁴ and a preliminary study has shown the safety and efficacy of CD30-directed CAR T cell therapy in cHL.³⁵ Recent studies have shown a potential positive impact for radiotherapy compared with systemic therapy as bridging treatment between leukapheresis and CAR-T cell infusion for large B-cell lymphoma,³⁶ while patients receiving high intensity chemotherapy as bridging therapy showed lower overall survival and increased rates of infection.³⁷ To our knowledge, no studies have assessed chemoimmunotherapy with checkpoint inhibitor plus BV as bridging therapy to CAR-T cell therapy. Based on the preliminary success of consolidative HCT in patients treated with nivolumab plus BV, this combination regimen could be considered as a bridging therapy for CAR T cell therapy in future studies in R/R lymphoma.

This study has a few limitations. The sample size was small (N = 30) and there is no comparator arm; this limits the interpretability of results and possibility of sub-group analyses and comparison with a control population. The study design evaluated only the efficacy and safety of nivolumab plus BV before consolidation; survival outcomes post-consolidation were not examined. There was also no central pathology review for efficacy assessment. Both median DOR and median OS were not reached in this extended follow-up, indicating that further long-term studies would provide more insight into survival outcomes.

Overall, this 3-year follow-up of the CheckMate 436 study shows durable safety and efficacy for nivolumab plus BV in patients with R/R PMBL and identifies no new safety signals. These

results support nivolumab plus BV as a salvage therapy option in PMBL, and this regimen could be considered as a bridging therapy for stem cell transplantation and CAR T cell therapy.

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Authorship

Contributions

Conception and design: A.S. Provision of study materials or patients: J.K. Collection and assembly of data: A.A. Data analysis and interpretation: A.S., J.K., N.M-S., A.A. Manuscript writing: P.L.Z., A.S., G.G., P.B., P.M.B., J.K., D.C., J.K., N.A.J., N.M-S., J.L., R.W., A.A., A.J.M. Final approval of manuscript: P.L.Z., A.S., G.G., P.B., P.M.B., J.K., D.C., J.K., N.A.J., N.M-S., J.L., R.W., A.A., A.J.M. Accountable for all aspects of the work: P.L.Z., A.S., G.G., P.B., P.M.B., J.K., D.C., J.K., N.A.J., N.M-S., J.L., R.W., A.A., A.J.M.

Conflicts of interest

P.L.Z reports honoraria from AstraZeneca, Bristol Myers Squibb, Gilead, Incyte, Kyowa Kirin, Merck, Novartis, Roche, Takeda, and Sanofi.

A.S. reports honoraria from Abbvie, Amgen, AstraZeneca, Bayer, Bristol Myers Squibb, Celgene, Eisai, Gilead, Lilly, Merck Sharp and Dohme, Novartis, Pfizer, Roche, Sandoz, Servier, and Takeda; advisory boards for Bayer, Bristol Myers Squibb, Eisai, Gilead, Merck Sharp and Dohme, and Pfizer, Servier; and consultancy for Incyte and Sanofi.

G.G. reports honoraria from Beigene, Clinigen, Ideogen, Incyte, Roche, and Takeda; advisory boards for Genmab, Ideogen, IQVIA, Italfarmaco, Kite–Gilead, Roche, and Takeda; consultancy for Takeda; and meeting/travel support from Roche and Sandoz.

P.B. reports honoraria from Takeda.

P.M.B. reports advisory boards for TG Therapeutics and consultancy for Abbvie, AstraZeneca, Beigene, Bristol Myers Squibb, Genentech, Gilead, Janssen, Merck, and TG Therapeutics.

J. Kuruvilla reports honoraria from Abbvie, Amgen, AstraZeneca, Bristol Myers Squibb, Gilead, Incyte, Janssen, Karyopharm, Merck, Novartis, Pfizer, Roche, and Seattle Genetics; advisory boards for Karyopharm; consultancy for Abbvie, Antengene, Bristol Myers Squibb, Gilead, Karyopharm, Medison Ventures, Merck, Roche, and Seattle Genetics; research support (institution) from AstraZeneca and Merck; and advisory board chair for Lymphoma Canada.

D.C. reports advisory boards for OVIBIO and research support (institution) from 4SC, Bayer, Celgene, Clovis, Eli Lilly, Leap, MedImmune, and Roche.

J. Kline reports honoraria from Kite–Gilead; consultancy for Merck, Morphosys, Seagen, and Secura Bio; and research support (institution) from Secura Bio.

N.A.J. reports honoraria from Abbvie and Beigene; consultancy for Abbvie, AstraZeneca, Beigene, Merck, Roche, and Seattle Genetics; research support from Incyte; and board membership for Lymphoma Canada.

N.M-S. reports consultancy for AstraZeneca, C4 Therapeutics, Daiichi Sankyo, Genentech/Roche, Karyopharm, Kyowa Kirin, Ono Pharmaceuticals, and Secura Bio/Verastem; and research support (institution) from AstraZeneca, Bristol Myers Squibb, Celgene, C4 Therapeutics, Corvus Pharmaceuticals, Daiichi Sankyo, Dizal Pharmaceuticals, Genetech/Roche, Innate Pharmaceuticals, Secura Bio/Verastem, and Yingli Pharmaceuticals.

J.L. is an employee and has stock in Seagen.

R.W. is a Bristol Myers Squibb employee.

A.A. is a Bristol Myers Squibb employee.

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Tables

Table 1. Baseline demographics and disease characteristics

Characteristic	Patients (N = 30)
Age, median (range), years	36 (19–83)
Female, n (%)	17 (56.7)
Disease stage at initial diagnosis, ^{*,†} n (%)	
I–II	16 (53.3)
III–IV	13 (43.3)
Disease status at enrollment, [†] n (%)	
Relapsed	7 (23.3)
Refractory	18 (60.0)
Relapsed and refractory [‡]	5 (16.7)
Prior lines of systemic therapy, median (range) ^{1,§}	2 (2–5)
First-line therapy, [§] n (%)	
R-CHOP	8 (26.7)
R-EPOCH	9 (30.0)
Other	13 (43.3)
Prior rituximab, [†] n (%)	30 (100.0)
Prior auto-HCT, [†] n (%)	4 (13.3)

HCT, hematopoietic cell transplantation; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; R-EPOCH, rituximab, etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin.

^{*}Disease stage at initial diagnosis not reported for one patient.

[†]Data from December 2020 database lock, presented at ICML 2021.³⁸

[‡]Defined as patients who relapsed after at least one prior line of therapy and had no response to the most recent prior therapy.

[§]These data are from January 2019 database lock.

^{||}Other anthracycline-containing therapies.

538 **Table 2. Best overall response per investigator**

Best overall response*	Patients (N = 30)
Objective response rate [†]	22 (73.3)
80% CI, %	60.3–83.8
95% CI, %	54.1–87.7
Complete response	12 (40.0)
Partial response	10 (33.3)
Stable disease	3 (10.0)
Relapsed or progressive disease	3 (10.0)
Unable to determine (death prior to disease assessment)	2 (6.7)

539 Data reported in n (%) unless otherwise stated.

540 *Based on Lugano Classification 2014.

541 [†]Confidence intervals based on the Clopper–Pearson method.

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543

544 **Table 3. Any-grade TRAEs reported in $\geq 10\%$ treated patients and grade 3/4 TRAEs in**
 545 **all treated patients with R/R PMBL**

Any-grade TRAEs reported in $\geq 10\%$ treated patients and grade 3/4 TRAEs in any patients, n (%)		Any grade	Grade 3/4
Total		25 (83.3)	16 (53.3)
Neutropenia		14 (43.3)	13 (40.0)
Pyrexia		9 (30.0)	1 (3.3)
Arthralgia		6 (20.0)	0
Thrombocytopenia		5 (16.7)	3 (10.0)
Rash		5 (16.7)	1 (3.3)
Peripheral sensory neuropathy		5 (16.7)	0
Peripheral neuropathy		4 (13.3)	3 (10.0)
Hyperthyroidism		4 (13.3)	0
Decreased neutrophil count		2 (6.7)	2 (6.7)
Colitis		1 (3.3)	1 (3.3)
Immune-mediated hepatitis		1 (3.3)	1 (3.3)
Maculopapular rash		1 (3.3)	1 (3.3)

546 PMBL, primary mediastinal B-cell lymphoma; R/R, relapsed/refractory; TRAE, treatment-
 547 related adverse event.

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549

550

Figure captions

Figure 1. Event chart for tumor response, tumor progression, duration of therapy, transplantation, and death for all responders with R/R PMBL, as assessed by investigator.

Horizontal bar indicates PFS.

CR, complete response; PFS, progression-free survival; PMBL, primary mediastinal B-cell lymphoma; PR, partial response; R/R, relapsed/refractory

Figure 2. Progression-free survival, per investigator, in all treated patients with R/R PMBL.

NR, not reached; PMBL, primary mediastinal B-cell lymphoma; R/R, relapsed/refractory.

Figure 3. Overall survival, per investigator, in all treated patients with R/R PMBL.

NR, not reached; PMBL, primary mediastinal B-cell lymphoma; R/R, relapsed/refractory.

Figure 1

▲ Censored ● PR ● CR × Transplant # Death
■ Last dose when patient off treatment

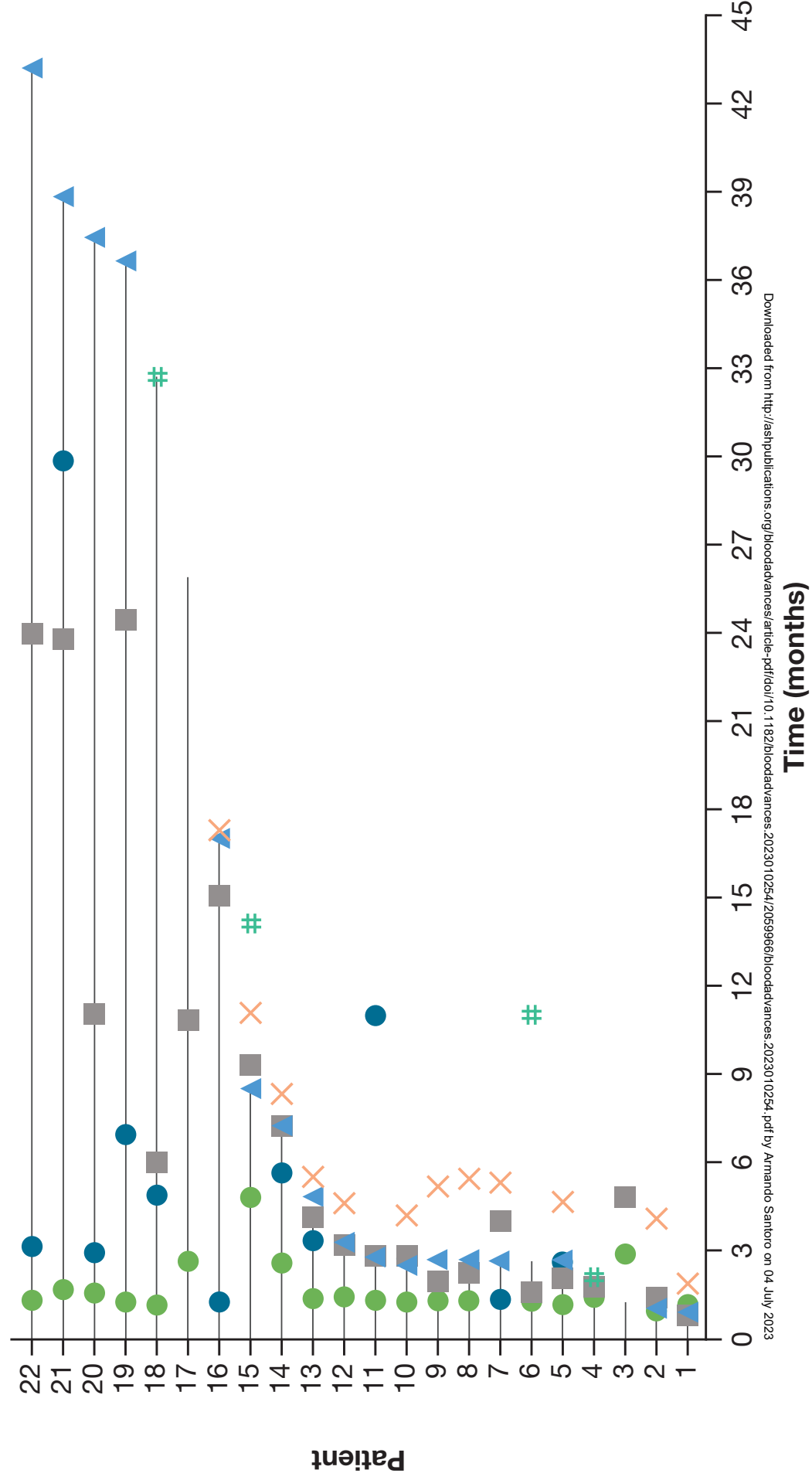
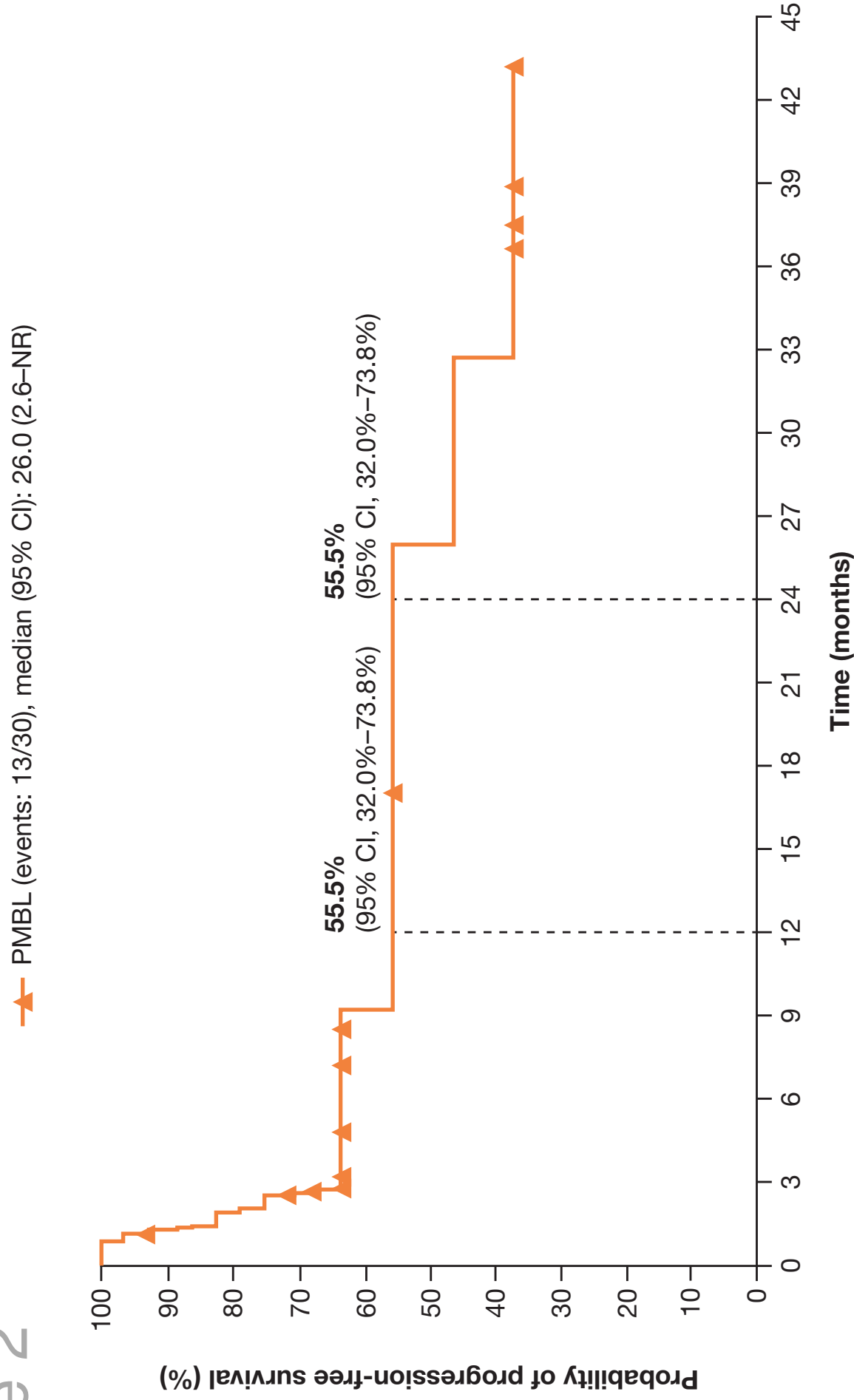


Figure 2



No. at risk
PMBL 30 12 10 8 7 7 7 6 6 6 5 4 4 1 1 0

